IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF NORTH CAROLINA
WESTERN DIVISION
No. 5:08-CV-00119-H

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|---|---|
| CELLECTIS SA, | ) |
| | ) |
| Plaintiff, | ) |
| | ) |
| v. | ) |
| | ) |
| PRECISION BIOSCIENCES, INC. | ) |
| | ) |
| Defendant. | ) |

**PRECISION BIOSCIENCES, INC.'S OPENING MEMORANDUM IN SUPPORT OF ITS PROPOSED CLAIM CONSTRUCTION**

## TABLE OF AUTHORITIES

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## I. INTRODUCTION

The claim construction position taken by Plaintiff Cellectis, SA ("Cellectis") presents a classic example of a patentee who made a narrow advance over the prior art, who then watched as the technology subsequently progressed in a different direction, and who now (through its licensee) seeks to have its patents read broadly to cover those subsequent inventions – even though those subsequent inventions are not described or taught anywhere in the patents, were not contemplated by the inventors at the time of their application, and do not fall within the scope of the claim language.

In sum, the patents-in-suit describe the use of a particular enzyme known as "I-SceI" to cut the DNA of an organism at a particular site – the naturally-occurring recognition site for the I-SceI enzyme. Because the recognition site is almost never found in the DNA of any organism in nature, this technique requires the artificial insertion of the I-SceI recognition site into the DNA of an organism to have any practical utility. That is the invention that was purportedly conceived by the named inventors in the early 1990s, and that was the invention originally claimed in the earliest (non-asserted) patents in the family.

As the state of the art improved, however, other inventors sought to develop methods of cutting the DNA of an organism without the major limiting step of having to first insert a recognition site. Some fifteen years after the purported inventions of the patents-in-suit, following major breakthroughs in the field, scientists at Precision BioSciences, Inc. ("Precision"), developed novel techniques of rationally designing and producing artificial enzymes that not only allowed for cutting DNA without prior insertion of a recognition site but also were engineered specifically to recognize and cut desired sequences of DNA. This rational design of enzymes to cut desired sequences directly would not have been scientifically possible at the time of the alleged inventions of the patents-in-suit in 1992 or 1994 and represented a quantum leap in the field of genetic engineering.

Soon after Cellectis was formed and took a license to the family of patents and patent applications covering the use of I-SceI in 2000, at a time when the changing direction of the genomic engineering field had become apparent, the prosecution strategy for the pending patent applications changed dramatically.

In light of the evolving technology, the applicants first improperly tried to broaden their claims beyond the scope of the original disclosure to include enzymes other than I-SceI, and to not require (expressly, at least) the prior insertion of the natural recognition site. In this litigation, Cellectis now attempts to expand the scope of the claimed invention even further by reading the claim language so broadly as to encompass the use of fundamentally different, non-naturally occurring, rationally-engineered enzymes that did not exist, and could not even have been developed either in 1992 or 1994. Because Cellectis's proposed reading of the claims is contrary to the actual claim language, specification, file histories, and the extensive extrinsic evidence, Cellectis's proposed claim constructions should be rejected by the Court.

Instead, the Court should adopt claim constructions that are commensurate with the scope of the inventions disclosed in 1992 and 1994, the time of the original applications to which the patents-in-suit claim priority, that are in agreement with the meaning the claim terms would have had to those of skill in the art in 1992 and 1994, that are consistent with the prosecution histories of the patents-in-suit (and related patent applications), and that are consistent with the inventors' and Cellectis's own statements over many years. For the reasons set forth below in more detail, Precision proposes claim interpretations that correctly embrace the proper scope of the claims.

## II. THE TECHNOLOGY AND PATENTS

### A. GROUP I INTRON ENCODED ENDONUCLEASES, HOMOLOGOUS RECOMBINATION, AND HOMING

U.S. Patent No. 6,610,545 ("the '545 Patent,") (Exhibit B to Cellectis SA's Complaint, Docket No. 1); and U.S. Patent No. 7,309,605 ("the '605 Patent,") (Exhibit A to Cellectis SA's Complaint, Docket No. 1) (collectively, the "Patents-in-Suit") are co-owned by the Institut Pasteur ("Pasteur") and the Université Pierre et Marie Curie ("UPMC") (collectively "the Patent Holders"). They are part of a family of patents ("the I-SceI Patents") by inventors Bernard Dujon *et al.*, which claim priority to patent applications first filed in 1992 and 1994. The I-SceI Patents were licensed by Cellectis in June 2000.

The Patents-in-Suit relate to methods for cutting the DNA of a living organism and inserting genes of interest. More specifically, they relate to (a) methods for *in vivo* site-directed genetic recombination in

an organism, and (b) methods for inducing at least one site-directed double-stranded break in the DNA of an organism, in which DNA is cut by one of a class of enzymes known as Group I intron encoded endonucleases ('545 Patent, Claim 7; '605 Patent, Claim 1.)

The Expert Declaration of Victoria Derbyshire, Ph.D. in Support of Defendant Precision Biosciences, Inc's Proposed Claim Constructions ("Derbyshire Decl."), Docket No. 59-12 filed in connection with the Joint Claim Construction Statement on January 16, 2009, provides a more detailed explanation of the background technology. The most salient points are the following:

- Group I intron encoded endonucleases are special enzymes that cut (or "cleave") double-stranded DNA (*i.e.*, they make a "double-stranded break") at a location in the DNA corresponding to a very specific DNA sequence, which is called the recognition site. (Derbyshire Decl., ¶¶ 18-20.)

- Like every enzyme or other protein produced in an organism, Group I intron encoded endonucleases are encoded by DNA. In the case of a Group I intron encoded endonuclease, the DNA that encodes it resides in a Group I intron. (Derbyshire Decl., ¶¶ 28, 37-39.)

- The DNA that encodes proteins is organized into genes. Typically, a gene consists of sections called exons separated by other sections called introns. In most cases, only exons – not introns – encode proteins. Thus, Group I intron encoded endonucleases are unusual in that they are encoded by introns, specifically Group I introns. (Derbyshire Decl., ¶¶ 28-31, 37-39.)

- Some versions (or "alleles") of a gene include a Group I intron (and are called "intron plus" or "In+"), while other versions of the same gene do not (and are called "intron minus" or "In-"). (Derbyshire Decl., ¶¶ 30, 35.)

- In the In+ allele, the intron is flanked on either side by an exon. In contrast, in the In- allele, the two exons abut one another directly to form an exon-exon junction. (Derbyshire Decl., ¶¶ 30, 35.)

- The exon-exon junction of the In- allele is referred to as the "intron insertion site," and is the location in the gene where the Group I intron would be inserted. (Derbyshire Decl., ¶¶ 35, 41.)

- The DNA sequence recognized by a particular Group I intron encoded endonuclease (its recognition site) includes the intron insertion site (defined by the exon-exon junction) for the Group I intron that encodes the particular Group I intron encoded endonuclease. (Derbyshire Decl., ¶ 39.)

- When a Group I intron encoded endonuclease finds its recognition site in the In- allele and cuts the DNA at that location, it can initiate a process called "homologous recombination." In "homologous recombination," the Group I intron is copied ("inserted") into the In- allele to form an In+ allele. This process is called "homing" because the Group I intron encoded endonuclease "homes" to its associated recognition site, cuts the DNA at that location, and results in conversion of the gene from the intron-less version to the intron-containing version, thus perpetuating the existence of the Group I intron and the endonuclease it encodes. (Derbyshire Decl., ¶¶ 32-33, 35, 39-42.)

- The recognition sites for Group I intron encoded endonucleases are typically at least 18 base pairs (*i.e.*, letters of genetic code) long. The statistical probability of the occurrence of specific sequence of

that length is roughly one in 69 billion base pairs, which is much larger than the entire genome of most organisms. (Derbyshire Decl., ¶¶ 119-120.)

- Because the recognition sites for Group I intron encoded endonucleases do not occur in the DNA of most organisms, using these enzymes to induce insertion of a gene of interest through homologous recombination requires prior insertion of the recognition site into the DNA of the target organism to enable the enzyme to cut the DNA. (Derbyshire Decl., ¶¶ 117, 126.)

Only with the advent in the last few years of rationally engineered enzymes designed expressly to recognize and cut particular predetermined, naturally occurring DNA sequences at or near target genes, has it become feasible to reliably perform highly efficient genetic engineering through homologous recombination without first inserting a recognition site. (Stoddard *et al.* (2008), Ex. A, at 139-40.)[1]

### B. THE I-SCEI PATENTS

#### 1. The I-SceI Patent Family

The original application in the I-SceI Patent family was USSN 07/879,689 ("the '689 Application"), filed May 5, 1992, which was abandoned. (*See* I-SceI Patent Family Tree, Ex. G.) Another application, USSN 07/971,160 ("the '160 Application"), was filed November 5, 1992 and forms the disclosure and specification for the '545 Patent. (*Id.*) A continuation-in-part of the '160 Application, USSN 08/336,241 ("the '241 Application"), filed November 7, 1994 (*id.*), includes additional subject matter not disclosed in the '160 Application, and forms the disclosure and specification for the '605 Patent.

#### 2. The Inventions and Claims of the I-SceI Patents

As the title of each of the I-SceI Patents indicates, the disclosed inventions are directed to a "Nucleotide Sequence Encoding the Enzyme I-SceI and the Uses Thereof." Long before the filing of the first application for the I-SceI Patents, Dujon *et al.* had discovered an endonuclease encoded by an intron in common baker's yeast, *Saccharomyces cerevisiae* (or *S. cerevisiae*) and had initially named the enzyme the "omega endonuclease." (Dujon *et al.* (1985), Ex. B.) The omega endonuclease was later renamed I-SceI, where the first "I" indicates that the enzyme is *i*ntron-encoded, the "Sce" indicates that the enzyme is found in *S. cerevisiae*, and the second "I" indicates that it is the first intron-encoded endonuclease found in that organism. (Dujon *et al.* (1989), Ex. C.) In the years between the discovery of

I-SceI and the filing of the first of the I-SceI Patents, other scientists discovered more Group I intron endonucleases, including those expressly listed in the claims.

Appropriately, given that the work by Dujon *et al.* was with I-SceI only, the originally filed claims in the earliest applications of the I-SceI Patents were limited to I-SceI or its use, reflecting the advance by by Dujon *et al*. Indeed, in ***every*** patent application in the I-SceI patent family before Cellectis was formed in 1999, ***all*** of the claims filed prior to the licensing of the patents to Cellectis were expressly limited to I-SceI or its use.

Shortly after Cellectis was formed in 1999, however, the Patent Holders first sought claims directed broadly to the use of "Group I intron encoded endonucleases" to cover the use of enzymes other than I-SceI, which had been discovered by others. In filing and prosecuting the '605 Patent at issue in this case, Cellectis sought to broaden the claims even further by omitting the step of inserting a recognition site for the enzyme, even though this step was essential to the practice of the disclosed inventions.

Through these actions and its claim construction positions in this case, Cellectis has attempted to expand the scope of their patent monopoly well beyond what the inventors disclosed, to cover revolutionary technology that they did not invent. The Court should not sanction that effort.

**C. Precision's Man-Made, Rationally-Designed Endonucleases**

Precision is engaged in the rational design of artificial enzymes with functionalities not found in naturally-occurring enzymes. Specifically, Precision develops rationally-designed endonucleases that recognize and cut desired DNA sequences that are substantially different from the sequences recognized and cut by Group I intron encoded endonucleases. Importantly, Precision's rationally-designed endonucleases are not encoded by Group I introns. More critically, this innovative technology does not require prior insertion of an endonuclease recognition site into the target DNA, thereby allowing for direct and precise manipulation of the gene of interest by targeting DNA sequences that already appear in the DNA of the organism. Precision's engineering of endonucleases to target predetermined sequences of the natural DNA of organisms with high efficiency and precision represents a highly significant advance in

[1] Exhibits refer to those attached to the Declaration of Allen Nunnally submitted herewith in support of this brief.

the state of the art and holds a wealth of potential applications, including human gene therapy. Most relevant for claim construction, Precision's technology is fundamentally different from the older I-SceI technology described in the Patents-in-Suit.

## III. BASIC PRINCIPLES OF CLAIM CONSTRUCTION

Claim construction is an issue of law for the court. *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 371-73 (1996). The Federal Circuit's *en banc* decision in *Phillips*, reaffirmed the basic principle that patent claims are to be given their ordinary and customary meaning "to a person of ordinary skill in the art in question at the time of the invention." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc). "The inquiry into how a person of ordinary skill in the art understands a claim term provides an objective baseline from which to begin claim interpretation." *Id.* "Because the meaning of a claim term as understood by persons of skill in the art is often not immediately apparent . . . the court looks to 'those sources available to the public that show what a person of skill in the art would have understood disputed claim language to mean.'" *Id.* at 1314 (quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Systems, Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004)). "Those sources include 'the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art.'" *Id.* (quoting *Innova*, 381 F.3d at 1116).

While "the best source for understanding a technical term is the specification from which it arose, informed, as needed, by the prosecution history," *Multiform Desiccants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1478 (Fed. Cir. 1998), the Federal Circuit has "also authorized district courts to rely on extrinsic evidence, which consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." *Phillips*, 415 F.3d at 1317 (quotation omitted). In particular, expert testimony may be used "to provide background on the technology at issue, to explain how an invention works, to ensure that the court's understanding of the technical aspects of the patent is consistent with that of a person of skill in the art, or to establish that a particular term in the patent or the prior art has a particular meaning in the pertinent field." *Id.* "However, conclusory,

unsupported assertions by experts as to the definition of a claim term are not useful to a court. Similarly, a court should discount any expert testimony that is clearly at odds with the claim construction mandated by the claims themselves, the written description, and the prosecution history, in other words, with the written record of the patent." *Id.* (quotation omitted).

## IV. ANALYSIS OF CLAIM TERMS[2]

### A. The '545 Patent

Cellectis has alleged infringement of Claims 7-16, 21-22 and 24-27 of the '545 Patent. Of these, only Claim 7 is an independent claim:

> 7. A method for in vivo site directed genetic recombination in an organism comprising:
>
> (a) providing a transgenic cell having at least one Group I intron encoded endonuclease recognition site inserted at a unique location in a chromosome;
>
> (b) providing an expression vector that expresses said endonuclease in said transgenic cell;
>
> (c) providing a plasmid comprising a gene of interest and a DNA sequence homologous to the sequence of the chromosome, allowing homologous recombination;
>
> (d) transfecting said transgenic cell with said plasmid of step (c);
>
> (e) expressing said endonuclease from said expression vector in said cell; and
>
> (f) cleaving said at least one Group I intron encoded endonuclease recognition site with said endonuclease, whereby said cleavage promotes the insertion of said gene of interest into said chromosome of said organism at a specific site by homologous recombination.

The terms requiring construction by the Court are: (i) "Group I intron encoded endonuclease" / "said endonuclease"; (ii) "Group I intron encoded endonuclease recognition site" / "said endonuclease recognition site"; (iii) "Class [I / II / III / IV / V] I-endonuclease site," (iv) "[I-SceI / I-SceIV / I-CsmI / I-PanI / I-CeuI / I-PpoI / I-CreI / I-TevI / I-TevII / I-TevIII] site"; (v) "A method for *in vivo* site-directed genetic recombination in an organism"; and (vi) "inserted at a unique location in a chromosome." The parties' alternative claim constructions for each of these terms are set forth in Exhibit D, and each of these terms is discussed separately below.

#### 1. "Group I intron encoded endonuclease" / "said endonuclease" [All Claims]

To support its allegations of infringement by Precision, Cellectis seeks to expand the meaning of

"Group I intron encoded endonuclease" to include "mutated or variant (including genetically engineered) Group I intron encoded endonucleases," with no limitations on the structure or sequence-specificity of the enzymes. This overly broad claim construction is necessary for Cellectis to assert the Patents-in-Suit against Precision's rationally-designed, genetically-engineered enzymes, which do not exist in nature and could not have been produced in 1992 or 1994 when the relevant patent applications were filed.

In contrast, Precision proposes the common-sense interpretation that a "Group I intron encoded endonuclease" is, in fact, as its name states, "an enzyme encoded by a Group I intron," and that it has the signature characteristic of a Group I intron-encoded endonuclease: It creates "a site-directed double-stranded break at or near the insertion site for that intron."

The claim language, the specifications, and the prosecution histories of the Patents-in-Suit support Precision's construction, not Cellectis's. The extrinsic evidence, including the inventors' own statements prior to filing of this lawsuit, is likewise consistent with Precision's proposed construction.

**a) The Claim Language and Specification**

Aside from the titles of the references listed at the end of the specification, the term "Group I intron encoded endonuclease" (or any variant thereof) appears in the specifications of the Patents-in-Suit exactly three times: once before the first table in column 10 of the '545 Patent[3], once in Figure 6, and once in the brief description of Figure 6. Moreover, aside from the titles of the references, the only mention of any Group I intron encoded endonucleases other than I-SceI (*i.e.*, I-SceII, I-SecIII, I-SceIV, I-PpoI, I-CeuI, I-CreI, I-CsmI, I-PanI, I-TevI, I-TevII, and I-TevIII) is in the two tables and accompanying text in column 10 of the '545 Patent (and, in the case of I-SceII, one additional reference in the Background of the Invention ('545 Patent, col. 2, lines 33-37).

'545 Patent, col. 10, lines 4-63 states:

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[2] The respective proposed claim constructions of the parties are shown on the chart attached hereto as Exhibit D.
[3] The specification of the '605 patent includes essentially all of the specification of the '545 Patent, as well as additional subject matter. All text cited in this brief in relation to the '545 Patent can be found identically in the '605 Patent, although the column and line numbers are displaced. Figures reference are identical in each patent.

Group I intron encoded endonucleases and related enzymes are listed below with references. Recognition sites are shown in FIG. 6.

| Enzyme | Encoded by | Ref |
|---|---|---|
| I-SceI | Sc LSU-1 intron | this work |
| I-SceII | Sc cox1-4 intron | Sargueil et al., NAR (1990) 18, 5659–5665 |
| I-SceIII | Sc cox1-3 intron | Sargueil et al., MGG (1991) 225, 340–341 |
| I-SceIV | Sc cox1-5a intron | Seraphin et al. (1992) in press |
| I-CeuI | Ce LSU-5 intron | Marshall, Lemieux Gene (1991) 104, 241–245 |
| I-CreI | Cr LSU-1 intron | Rochaix (unpublished) |
| I-PpoI | Pp LSU-3 intron | Muscarella et al., MCB (1990) 10, 3386–3396 |
| I-TevI | T4 td-1 intron | Chu et al., PNAS (1990) 87, 3574–3578 and Bell-Pedersen et al. NAR (1990) 18, 3763–3770. |
| I-TevII | T4 sunY intron | Bell-Pedersen et al. NAR (1990) 18, 3763–3770. |
| I-TevIII | RB3 nrdB-1 intron | Eddy, Gold, Genes Dev. (1991) S, 1032–1041 |
| HO | HO yeast gene | Nickoloff et al., MCB (1990) 10, 1174–1179 |
| Endo SceI | RF3 yeast mito. gene | Kawasaki et al., JBC (1991) 266, 5342–5347 |

Putative new enzymes (genetic evidence but no activity as yet) are I-CsmI from cytochrome b intron 1 of *Chlaydomonas smithii mitochondria* (ref. 15), I-PanI from cytochrome b intron 3 of *Podospora anserina* mitochondria (Jill Salvo), and probably enzymes encoded by introns Nc nd1*1 and Nc cob*! from *Neurospora crassa.*

The I-endonucleases can be classified as follows:

Class I: Two dodecapeptide motifs, 4 bp staggered cut with 3' OH overhangs, cut internal to recognition site

| Subclass "I-SceI" | Other subclasses |
|---|---|
| I-SceI | I-SceII |
| I-SceIV | I-SceIII |
| I-CsmI | I-CeuI (only one dodecapeptide motif) |
| I-PanI | I-CreI (only one dodecapeptide motif) |
| | HO |
| | TFP1-408 (HO homolog) |
| | Endo SceI |

Class II: GIY-($N_{10-11}$) YIG motif, 2 bp staggered cut with 3' OH overhangs, cut external to recognition site:
I-TevI

Class III: no typical structural motifs, 4 bp staggered cut with 3' OH overhangs, cut internal to recognition site:
I-PpoI

Class IV: no typical structural motifs, 2 bp staggered cut with 3' OH overhangs, cut external to recognition site:
I-TevII

Class V: no typical structural motifs, 2 bp staggered cut with 5' OH overhangs:
I-TevIII.

'545 Patent, Fig. 6. shows "Group I intron encoding endonucleases and related endonucleases":

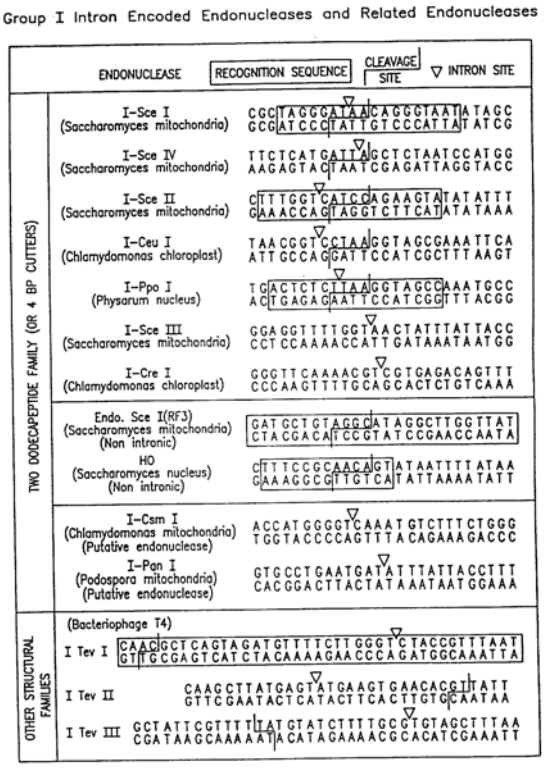


FIG. 6

As shown above, when referring to "Group I intron encoded endonucleases," the patent

specifications expressly associate them with ten specific endonucleases ("[e]nzymes"),[4] which are "[e]ncoded by" particular and definite corresponding introns. This is, of course, consistent with Precision's proposed claim construction that a Group I intron encoded endonuclease is "an enzyme encoded by a Group I intron" and inconsistent with Cellectis's proposed construction, which is not limited to any specific structure and does not require intron-encoded endonucleases to be encoded by introns. (*See also* Derbyshire Decl., ¶¶ 63, 71.)

The specifications also support Precision's proposed limitation that a Group I intron encoded endonuclease "creates a site-directed double-stranded break at or near the insertion site for that intron." Thus, immediately preceding the first table, the specifications state that "Recognition sites are shown in FIG. 6." ('545 Patent, col. 10, lines 5-6.) For each of the disclosed Group I intron encoded endonucleases, Figure 6 shows one or more of the "RECOGNITION SEQUENCE,"[5] "CLEAVAGE SITE," AND "INTRON SITE."[6] ('545 Patent, Fig. 6.)

Several points regarding Figure 6 are significant: (a) The recognition site of ***every*** enzyme is shown as including the "intron site" (shown as an inverted triangle), and thus, for every enzyme listed, the recognition site is identified as a segment of DNA having a sequence of base pairs flanking the insertion site of the intron encoding the endonuclease; (b) the particular location of the cleavage sites (shown as staggered lines through the sequences) have been identified for only eight of the Group I intron encoded endonucleases (*i.e.*, I-SceI, I-SceII, I-SceIV, I-Ceu, I-PpoI, I-TevI, I-TevII and I-TevIII); (c) the boundaries of the recognition sequences (shown as boxes around the sequences) have been identified for only four of the Group I intron encoded endonucleases (*i.e.*, I-SceI, I-SceII, I-PpoI and I-TevI), and (d) neither the cleavage sites nor the boundaries of the recognition sequences were defined for the remaining four Group I intron encoded endonucleases (*i.e.*, I-SceIII, I-CreI, I-CsmI and I-PanI).

In sum, the only information available and provided in the specifications for each Group I intron encoded endonuclease was the location of the insertion site for the Group I intron. Thus, the only basis

[4] The table also lists two endonucleases that are not intron encoded: HO and EndoSceI.
[5] The specifications use the term "recognition site" and "recognition sequence" interchangeably.

provided in the specification for describing the sequences of Figure 6 as "recognition sites" is that they include the insertion site. This is consistent with Precision's proposed claim construction that a Group I intron encoded endonuclease is "an enzyme encoded by a Group I intron that creates a site-directed double-stranded break at or near the insertion site for that intron," and inconsistent with Cellectis's proposed construction which requires nothing except, perhaps, the ability to cut DNA.

**b) Prosecution History**

Although the prosecution histories of the I-SceI Patents do not directly address the term "Group I intron encoded endonuclease," they contain no evidence that either the Patent Holders or the U.S. Patent and Trademark Office ("PTO") ever contemplated that the term could include a "mutated or variant (including genetically engineered)" Group I intron encoded endonuclease as Cellectis now suggests.

**c) Extrinsic Evidence**

In addition to the claim language itself and the teachings of the specifications, contemporaneous scientific literature, including a reference co-authored by some of the named inventors of the Patents-in-Suit, makes clear that researchers in the field, including the inventors, interpreted the term Group I intron encoded endonucleases in a manner consistent with Precision's proposed constructions. For example, Perrin *et al*. (1993), co-authored by named inventors Arnaud Perrin and Bernard Dujon, states (Ex. E, at 2944 (emphasis added)):

> It has also been shown by extensive mutagenesis that the homing endonuclease I-SceI recognizes an unusually long non-palindromic nucleotide sequence consisting of the junction between the two exons in the intron-less gene (Colleaux et al., 1988). The same applies to other homing endonucleases subsequently studied . . .
>
> * * *
>
> Like all known intron-encoded endonucleases, I-SceI recognizes a long and asymmetrical site made of the junction between two exons in the intron-less form of the gene.

Thus, as shown in the excerpt above, in the early- to mid-1990s, those of skill in the art, including named inventors of the Patents-in-Suit, understood a Group I intron encoded endonuclease, such as I-

[6] The specifications use the term "intron site" and "intron insertion site" interchangeably.

SceI, to be an enzyme which cuts DNA at or near the insertion site for that intron (*i.e.*, "the junction between the two exons in the intron-less gene"). (*See also* Derbyshire Decl., ¶ 62.)

Therefore, Precision's proposed claim construction of the term "Group I intron encoded endonuclease" as "an enzyme encoded by a Group I intron that creates a site-directed double-stranded break at or near the insertion site for that intron" is entirely consistent with the claim language, specifications, and prosecution histories of the Patents-in-Suit, as well as the understanding of those of skill in the art in 1992 and 1994, as indicated by the published statements of the inventors themselves as well as by the declaration of Precision's expert, Dr. Derbyshire.

**d) Cellectis's Flawed Construction**

In contrast, Cellectis has suggested that the term "Group I intron encoded endonuclease" should be defined as a "naturally occurring (wild-type) and mutated or variant (including genetically engineered) Group I intron encoded endonuclease." This definition is not supportable.

First, genetically-engineered enzymes are not encoded by Group I introns. On the contrary, they are, by definition, encoded by DNA molecules which have been artificially created by scientists in a laboratory. (Derbyshire Decl., ¶ 71.) Thus, Cellectis's proposed construction of this term is directly contrary to plain claim language because it requires the term Group I intron encoded endonuclease to include endonucleases which are ***not*** encoded by Group I introns. Such a construction is improper because it would render meaningless the phrase "Group I intron encoded." *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1372 (Fed. Cir. 2005) ("A claim construction that gives meaning to all the terms of the claim is preferred over one that does not do so."); *Elekta Instrument S.A. v. O.U.R. Sci. Int'l, Inc.*, 214 F.3d 1302, 1307 (Fed. Cir. 2000) (construing claim to avoid rendering limitation superfluous).

Such a construction is also not consistent with the usage in the art and, in fact, Cellectis's expert, Dr. Stoddard, admitted as much in his deposition. Specifically, Dr. Stoddard testified that he had created a genetically engineered endonuclease based upon the Group I intron encoded endonucleases I-DmoI and I-CreI (in which the first "I" indicates that the enzymes are intron encoded). Dr. Stoddard named the new enzyme "E-DreI," in which the "DreI" was a blend of "DmoI" and "CreI." Significantly, the "E" was

used to indicate that it is engineered, rather than an "I," which would have indicated that it was intron-encoded. (Stoddard Dep. Tr., Ex. F, at 56:6-59:11.) Thus, Cellectis's own expert specifically avoided the "I" designation that would have falsely suggested the engineered endonuclease was intron-encoded.

In addition, Cellectis's proposed claim construction is hopelessly vague and indefinite because the proposed terms "mutated" and "variant" are open-ended. (Derbyshire Decl., ¶ 69, 73.)[7] That is, if one were to insert, delete and/or substitute enough amino acids in the sequence of one protein, one could produce the sequence of any other protein (just as one could change any word into any other word by inserting, deleting and/or substituting enough letters). As a result, any endonuclease could be regarded as a "mutated" or "variant" form of any other, and the term "Group I intron encoded endonuclease" would thereby be rendered meaningless. (Derbyshire Decl., ¶ 72.)

Finally, although they use slightly different phrasing, both parties interpret the phrase "said endonuclease" as referring to the Group I intron encoded endonuclease mentioned earlier in the claims.

**2. "Group I intron encoded endonuclease recognition site" / "said endonuclease recognition site" [All Claims]**

Just as one skilled in the art in 1992 or 1994 would have understood that a Group I intron encoded endonuclease creates a site-directed double-stranded break at or near the insertion site of the corresponding Group I intron, one of skill in the art would have understood that the "recognition site" is the DNA sequence that includes the insertion site, and that is recognized and cut by the endonuclease. Thus, Precision has proposed the common sense claim construction that the term "Group I intron encoded endonuclease recognition site" means "a segment of DNA having a sequence that is recognized by a Group I intron encoded endonuclease, and that includes the insertion site for the corresponding Group I intron."

**a) The Claim Language and Specification**

[7] While there may, of course, be naturally-occurring "mutated and variant" forms of the Group I intron encoded endonucleases (Derbyshire Decl., ¶ 70), to the extent such mutants and variants are encoded by Group I introns and would create a site-directed double-stranded break at or near the insertion sites for the introns that encode them, they would be "Group I intron encoded endonucleases" within the scope of Precision's proposed claim construction.

The claim language refers to the "site" (or sequence) that is recognized by a "Group I intron encoded endonuclease." The sites recognized by various Group I intron encoded endonucleases are described in the specification. In particular, consistent with Precision's claim construction, the specifications states: "The recognition site corresponds, in part, to the upstream exon and, in part, to the downstream exon of the intron plus form of the gene." ('545 Patent, col. 6, lines 63-65). Thus, the inventors themselves describe the recognition site as corresponding to the segment of DNA formed by the junction of the exons that would flank the corresponding intron if it were present. Because this exon-exon junction defines the intron insertion site, the inventors teach that the recognition site necessarily includes the intron insertion site.

Figure 6 of the specification confirms this interpretation: As noted above, for ***every*** Group I intron encoded endonuclease, it shows the insertion site of the corresponding Group I intron (*i.e.*, "intron site") within the recognition site.

**b) Prosecution History**

The prosecution histories of the I-SceI Patents do not contain any language contrary to Precision's proposed construction based on the plain meaning of the claim language.

**c) Extrinsic Evidence**

The contemporary scientific literature likewise supports Precision's claim construction. As described above, the 1993 Perrin *et al*. reference, co-authored by named inventors Arnaud Perrin and Bernard Dujon, explains that I-SceI and "all known intron-encoded endonucleases . . . recognize[ ] a long and asymmetrical site made of the junction between two exons in the intron-less form of the gene." (Ex. E., Perrin *et al*. (1993) at 2939, 2944.):

For these reasons, one of skill in the art would conclude that the term "Group I intron encoded endonuclease recognition site" means a "segment of DNA having a sequence that is recognized by a Group I intron encoded endonuclease, and that includes the insertion site for the corresponding Group I intron." (Derbyshire Decl., ¶¶ 75-86.)

**d) Cellectis's Flawed Construction**

In contrast, Cellectis again proposes an interpretation that renders the claim term "Group I intron encoded endonuclease recognition site" essentially meaningless (Derbyshire Decl., ¶ 87) and that is not supported by the claim language, the specifications, or the prosecution history. In particular, Cellectis proposes that the term means any "DNA site in the chromosome that is recognized by a naturally occurring or mutated or variant (including genetically engineered) Group I intron encoded endonuclease."

First, in an obvious attempt to avoid the prior art, Cellectis proposes to limit the recognition site to DNA sites which are present "in the chromosome." This is inconsistent with the express claim language. Step (a) of Claim 7 of the '545 Patent specifies "providing a transgenic cell having at least one Group I intron encoded endonuclease recognition site inserted at a unique location in a chromosome." Thus, Cellectis's proposed claim construction would be redundant to the existing claim language in the '545 Patent and would render the claim language "in a chromosome" in Claim 7 meaningless. Such a construction is improper. *Merck*, 395 F.3d at 1372; *Elekta*, 214 F.3d at 1307.

In the '605 Patent, by contrast, Claim 1 of that patent does not specify that the recognition site is "in the chromosome" at all, and, therefore, Cellectis's proposed construction asks the Court to read in a limitation that is not in the claims. Such importation of limitations into the claims is inappropriate. *Comark Commc'ns, Inc. v. Harris Corp.*, 156 F.3d 1182, 1186 (Fed. Cir. 1998).

Next, Cellectis repeats its attempt to expand the scope of the claims by asking the Court to construe the otherwise narrow claims as including recognition sites that are recognized by "mutated or variant (including genetically engineered)" endonucleases. This proposed construction should be rejected for the same reasons set forth in connection with the construction of "Group I intron encoded endonucleases" above: (a) genetically-engineered endonucleases are not intron encoded, and (b) the terms "mutated or variant" are vague, indefinite and open-ended.

Furthermore, Cellectis's proposed inclusion of the phrase "mutated or variant (including genetically-

engineered)" should be rejected because a definition which excludes nothing fails as a definition.[8] As described by Dr. Derbyshire, with sufficient inventive effort, a genetically-engineered endonuclease could be produced which recognizes virtually any DNA sequence. (Derbyshire Decl., ¶ 91.) For example, the naturally-occurring I-CreI endonuclease has a recognition site of 18 base pairs, for which the inventors disclosed one single, natural recognition site. (*See* '545 Patent, Fig. 6.) But according to Cellectis's proposed claim construction, an I-CreI recognition site could encompass ***all 68,719,476,736*** possible combinations of nucleotides in an 18 base pair sequence.[9] (Derbyshire Decl., ¶ 91.) Even Dr. Stoddard acknowledged that, under Cellectis's proposed claim construction, he did not know whether there was *any* "theoretical or empirical limit" on the number of potential recognition sites for a Group I intron encoded endonuclease. (Stoddard Dep. Tr., Ex. F, at 138:23-139:4.)

Finally, both parties interpret the term "said endonuclease recognition site" as having the same meaning as "Group I intron encoded endonuclease recognition site."

**3. "[Class I / Class II / Class III / Class IV / Class V] I-endonuclease site(s)" [Claims 13 and 14]**

The parties agree that the specifications of the Patents-in-Suit define Class I, Class II, Class III, Class IV, and Class V endonuclease sites in terms of structure and function. (*See* '545 Patent, col. 10, lines 38-63.) For example, the specifications define Class II I-endonucleases as having "GIY-($N_{10-11}$) YIG motif, 2 bp staggered cut with 3' OH overhangs, cut external to recognition site: I-TevI." ('545 Patent, col. 10, lines 51-53.)

Both parties incorporate the limitations of these definitions into their respective proposed claim constructions for the term "Group I intron encoded endonuclease recognition site." Thus, the differences between the parties' proposed constructions of the terms "Class [I / II / III / IV / V] I-endonuclease" can be reduced to the differences between the parties' proposed constructions of the term "Group I intron

8 As noted previously, there may, of course, be naturally-occurring "mutated and variant" forms of the Group I intron encoded endonucleases. The recognition sites of such mutants and variants, however, fall within the scope of Precision's proposed claim construction for the term "Group I intron encoded endonuclease recognition site."

9 The number of possible 18 base sequences of 4 possible bases is $4^{18}$ = 68,719,476,736.

encoded endonuclease recognition site."

**4. "[I-SceI / I-SceIV / I-CsmI / I-PanI / I-CeuI / I-PpoI / I-CreI / I-TevI / I-TevII / I-TevIII] site" [Claims 15-19, 21-22, 24-27]**

With respect to the terms "[I-SceI / I-SceIV / I-CsmI / I-PanI / I-CeuI / I-PpoI / I-CreI / I-TevI / I-TevII / I-TevIII] site," the difference between the parties' proposed constructions again parallels the differences between their constructions of "Group I intron encoded endonuclease recognition site." For all the reasons set forth above, Precision's proposed construction of "Group I intron encoded endonuclease recognition site" is the correct one.

**5. "A method for *in vivo* site-directed genetic recombination" [All Claims]**

There are two main differences between the parties' alternative claim constructions: (1) Precision construes the term "genetic recombination" as involving insertion of a gene of interest into any DNA of a cell, whereas Cellectis limits it to insertion into chromosomal DNA; and (2) Precision construes the term "site-directed" as meaning "into a pre-determined location," whereas Cellectis seems to suggest that "site-directed" includes any location where a cleavage site may be (randomly or non-randomly) present. This intrinsic evidence supports Precision's proposed construction.

**a) Claim Language**

With respect to the term "genetic recombination," the claim language supports construing "genetic recombination" in accordance with the plain meaning of that term and is inconsistent with limiting that term to insertion of a gene of interest into "chromosomal DNA." Step (a) of Claim 7 of the '545 Patent expressly provides that the recognition site is inserted "in a chromosome" and step (f) similarly provides that the gene of interest is inserted "into said chromosome." If, the term "genetic recombination" required insertion into chromosomal DNA, as Cellectis proposes, the claim language specifying insertion into the chromosome would be redundant and add no meaning. Such a construction of "genetic recombination" cannot be proper. *Merck*, 395 F.3d at 1372; *Elekta*, 214 F.3d at 1307.

Likewise, the claim language demonstrates that the term "site-directed" means "into a predetermined location," as Precision proposes. Step (c) of Claim 7 of the '545 Patent requires

"providing a plasmid comprising a gene of interest and a DNA sequence homologous to the sequence of the chromosome" to promote homologous recombination. By definition, homologous recombination involves DNA molecules that have segments or regions with identical or similar (*i.e.*, "homologous") base sequences. (Derbyshire Decl., ¶ 33). Therefore, it is necessary that the relevant sequence of the chromosome be known in advance, such that the gene of interest can be targeted to the pre-determined location of that sequence by using the homologous sequence required in step (c). Further, step (f) of Claim 7 requires "cleaving said at least one Group I intron encoded endonuclease recognition site with said endonuclease, whereby said cleavage promotes the insertion of said gene of interest into said chromosome of said organism ***at a specific site*** by homologous recombination," confirming that "site-directed" means "into a predetermined location." (emphasis added.)

**b) Specification**

The specification provides extensive support for Precision's proposed construction of "genetic recombination" as involving insertion of a gene of interest into any DNA, not merely chromosomal DNA as Cellectis proposes. As described above, Group I intron encoded endonucleases cut the intron-less version of a gene and, thereby, promote homologous recombination, resulting in the insertion of the corresponding Group I intron into that gene. The specification, including the references which are "incorporated by reference" therein, demonstrates that several Group I intron encoded endonucleases are encoded by introns found in the DNA of mitochondria and chloroplasts, which is ***not*** chromosomal DNA of the cell. (*See* '545 Patent, col. 10, lines 4-40 & col. 20, line 1 – col. 24, line 18.) For example, I-SceI, I-SceII, I-SceIII and I-CeuI are encoded by the "Sc LSU-1 intron," "Sc cox1-4 intron," "Sc cox1-3 intron" and "Ce LSU-5 intron," respectively. ('545 Patent, col. 10, lines 4-40.) These introns are present in mitochondrial DNA of the yeast *Saccharomyces cerevisiae*, or the chloroplast DNA of the algae *Chlamydomonas eugametos*, (Dujon *et al.* (1989), Ex. C, Table I), none of which is chromosomal DNA. Thus, the teachings of the specification are clearly consistent with Precision's proposed construction that the term "genetic recombination" occurs in any DNA, and is not limited to chromosomal DNA.

The specification also confirms that the term "site-directed" means "into a predetermined location."

First, the specification expressly distinguishes between "site-directed . . . homologous recombination" and random integration of a recognition site at any location:

> 2. Insertion of Artificial Sites
>
> Given the absence of natural I-SceI sites, artificial sites can be introduced by transformation or transfection. Two cases need to be distinguished: site-directed integration by homologous recombination and random integration by non-homologous recombination, transposon movement or retroviral infection.

('545 Patent, col. 14, lines 45-51.)

Second, the specification states that "FIG. 19 depicts diagrams of successful *site directed* homologous recombination experiments performed in yeast." ('545 Patent, col. 5, lines 66-67 (emphasis added). Figure 19 is reproduced below:

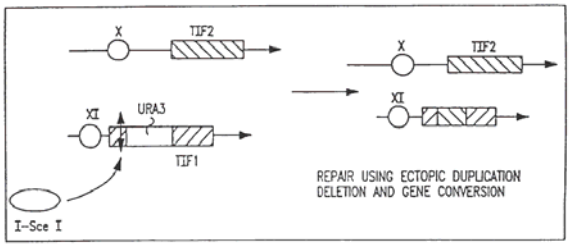


FIG. 19A

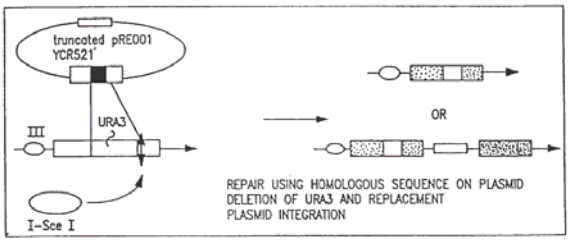


FIG. 19B

Figure 19A shows a segment of the DNA labeled "TIF2" from the chromosome labeled "X" is inserted into the chromosome labeled "XI" (replacing the "URA3" segment) at a pre-determined location (*i.e.*, the chromosome XI TIF1 gene). Similarly, Figure 19B shows a segment of DNA from the plasmid labeled "pRE001" was inserted into the chromosome labeled "III" (replacing the URA3 segment) at a pre-determined location in the chromosome III YCR521 gene. In both cases, the I-SceI recognition site (indicated by a double-ended arrow) was also inserted by homologous recombination at a pre-determined location (in the chromosome XI TIF1 gene in Fig. 19A and in chromosome III YCR521 gene in Fig.

19B). If the I-Sce recognition site had not been inserted at a pre-determined location in each example, it would not have been possible to insert the gene of interest at or near the recognition site. (*See* Derbyshire Decl., ¶¶ 56-58.)

**c) Prosecution History**

The prosecution histories of the I-SceI Patents contain nothing inconsistent with Precision's proposed construction for the term "a method for in vivo site-directed genetic recombination."

**d) Extrinsic Evidence**

As explained by Dr. Derbyshire, the term "site-directed" had a specific meaning to those of skill in the art in 1992 and 1994. (Derbyshire Decl., ¶ 52) Specifically, the term "site directed" was used to distinguish genetic recombination which occurs at a pre-determined location in a DNA molecule from genetic recombination which occurs at a random location in a DNA molecule. (*Id.*) In this context, according to Dr. Derbyshire, the "location" or "site" of the recombination is specified by a particular DNA sequence that is determined before practicing the claimed method. (*Id.*)

**e) Cellectis's Flawed Construction**

First, Cellectis's attempt to limit the term "genetic recombination" to insertion of a gene of interest into chromosomal DNA should be rejected because, as described above, (a) the specification and references incorporated therein teach that Group I intron encoded endonucleases promote genetic recombination at naturally-occurring recognition sites in DNA other than chromosomal DNA, such as mitochondrial and chloroplast (non-chromosomal) DNA, and (b) interpreting the term "genetic recombination" to require insertion in chromosomal DNA would render redundant and meaningless the claim language specifying that the recognition site and insertion are "in the chromosome" of the organism. *Merck*, 395 F.3d at 1372 (holding that all claim terms should be given meaning).

Second, with respect to the claim term "site-directed," Cellectis' proposed claim construction should be rejected because it gives no meaning to this term, suggesting only that the genetic recombination occurs "at the cleavage site," with no indication that the recognition site (including the cleavage site) has been inserted in a site-directed manner. *Id.*

### 6. "Inserted at a unique location in a chromosome"

There is only one significant difference between the parties' proposed constructions of the term "inserted at a unique location in a chromosome": Precision proposes that the term "unique" means "single" whereas Cellectis seeks to effectively eliminate the term "unique" from the claim as there is nothing in Cellectis' proposed construction which could possibly have the meaning of "unique."

#### a) The Claim Language and Specification

The term "inserted at a unique location in a chromosome" is used only once in the specifications of the Patents-in-Suit, in the context of strategies for the "site-specific insertion of a DNA fragment from a plasmid into a chromosome" ('545 Patent, col. 19, lines 43-53, emphasis added):

> Several strategies can be attempted for the ***site specific insertion*** of a DNA fragment from a plasmid into a chromosome . . .
>
> -1- Construction of a transgenic cell in which the I-SceI recognition site is ***inserted at a unique location in a chromosome***. Cotransformation of the transgenic cell with the expression vector and ***a*** plasmid containing the gene of interest and ***a*** segment homologous to ***the*** sequence in which the I-SceI site is inserted.

In this context, it is clear that the I-SceI site is inserted at a single location because (a) the method is described as "site-specific," indicating that the method is targeted to a single, specific site, (b) the method employs *a* plasmid with *a* sequence homologous to *the* sequence in which *the* I-SceI site is inserted, indicating that the method is targeted to a single, specific site. In contrast, if there were multiple locations at which the I-SceI site were inserted, the method would not be site-specific and would require multiple plasmids with multiple sequences homologous to multiple insertion sites.

#### b) Prosecution History

The prosecution history of the '545 Patent contains nothing inconsistent with Precision's proposed construction for the term "inserted at a unique location in a chromosome."

#### c) Cellectis's Flawed Interpretation

Cellectis's proposed construction should be rejected because it unjustifiably seeks to re-write the claims to effectively eliminate the term "unique," as there is nothing in Cellectis's proposed construction which could possibly have the meaning of "unique." *Merck*, 395 F.3d at 1372 (holding that all claim

terms should be given meaning).

**B. The '605 Patent**

Cellectis has alleged infringement of Claims 1, 6-7, and 9-17 of the '605 Patent. Of these, only Claim 1 is an independent claim:

> 1. A method for inducing at least one site directed double-stranded break in the DNA of an organism comprising:
>
> (a) providing an isolated cell of said organism containing at least one Group I intron encoded endonuclease recognition site at a location in the DNA of the cell,
>
> (b) providing said Group I intron encoded endonuclease to said cell by genetically modifying the cell with a nucleic acid comprising said Group I intron encoded endonuclease or by introducing said Group I intron encoded endonuclease protein into the cell such that the Group I intron encoded endonuclease cleaves said Group I intron encoded endonuclease site at the location in the DNA of the cell.

The terms of the asserted claims of the '605 Patent whose meaning requires construction by the Court are as follows: (i) "Group I intron encoded endonuclease" (all claims); (ii) "Group I intron encoded endonuclease recognition site" / "Group I intron encoded endonuclease site" (all claims); (iii) "[I-CeuI / I-PpoI / I-CreI / I-TevI / I-TevII / I TevIII / I-SceI] site" (claims 6, 7, 9-13); (iv) "A method for inducing at least one site-directed double-stranded break in the DNA of an organism"; (v) "containing at least one Group I intron encoded endonuclease recognition site"; (vi) "a location in the DNA of the cell;" (vi) "DNA of the cell" / "DNA of said cell" / "DNA of an organism" / "DNA of said organism"; and (vii) "at a unique location in the genome." The parties' respective claim constructions for each of these terms are set forth in Exhibit D, and each of these terms is discussed separately below.

Precision's constructions of "Group I intron encoded endonuclease," "Group I intron encoded endonuclease recognition site" / "Group I intron encoded endonuclease site," "[I-CeuI / I-PpoI / I-CreI / I-TevI / I-TevII / I-TevIII / I-SceI] site" are correct for the reasons set forth in Sections IV.A.1-2, 4 *supra*.

**1. "A method for inducing at least one site-directed double-stranded break in the DNA of an organism" [All Claims]**

There are two main differences between the parties' alternative claim constructions: (1) consistent with the plain meaning of the phrase, Precision construes the term "DNA of an organism" as being the

"heritable genetic material of an organism," whereas Cellectis construes it narrowly as "chromosomal DNA of an organism's cell"; and (2) Precision construes the term "site-directed" as "where the location ... is pre-determined," whereas Cellectis omits the term or any equivalent from its proposed claim construction. The claim language, specification, prosecution histories of related patent applications, and extensive extrinsic evidence support Precision's proposed constructions of these terms.

**a) Claim Language**

Nowhere in the language of Claim 1 of the '605 Patent is there any indication that the inventors intended to limit the claimed method to inducing a double-stranded break in a chromosome. The word "chromosome" does not even appear in that claim. In contrast, Claim 7 of the '545 Patent explicitly states that the cleavage "promotes the insertion of said gene of interest into said chromosome." Thus, when the inventors intended to limit the scope of their claims to chromosomal DNA, they did so. As such it would be improper now to read that omitted limitation into the claim language. *NTP, Inc. v. Research in Motion, Ltd.*, 418 F.3d 1282, 1293 (Fed. Cir. 2005) ("Because [plaintiff's] patents all derive from the same parent and share many common terms, we must interpret the claims consistently across the patents."); *see also Intertrust Techs. Corp. v. Microsoft Corp.*, 275 F. Supp. 2d 1031, 1055 (N.D. Cal. 2003) (holding that where limitation is expressly contained in related patent claims, such limitation should not be implicitly read into claims).

**b) Specification**

The specification likewise is consistent with Precision's proposed construction of "DNA of an organism" and inconsistent with Cellectis's. As explained in Section IV.A.5 *supra*, the specification discloses that Group I intron encoded endonucleases induce genetic recombination and double-stranded breaks at recognition sites in mitochondrial DNA and chloroplast DNA – which are both part of the heritable genetic material of an organism but not in the chromosomal DNA of an organism. Moreover, the '605 Patent teaches three strategies "for the site specific insertion of a DNA fragment from a plasmid into a chromosome." ('605 Patent, col. 22, lines 33-54.) Two of these three strategies involve an I-SceI recognition site inserted next to or within a gene of interest carried on a plasmid (which is non-

chromosomal DNA). (Derbyshire Decl., ¶ 16.) Therefore, the specification clearly teaches that double-stranded breaks can be induced in non-chromosomal DNA.

With respect to the term "site directed," as explained in Section IV.A.5, *supra*, the specifications clearly distinguishes between "site directed" and "random" insertion of recognition sites ('605 Patent, col. 17, lines 24-30) and depict "site-directed" recombination in which the double-stranded break is induced at a recognition site inserted at a pre-determined location. ('605 Patent, Figure 19.)

**c) Prosecution History**

The inventors' statements during prosecution of a related patent application demonstrate that the phrase "in the DNA of an organism" means any DNA and is not limited to "chromosomal DNA." During the prosecution of USSN 08/336,241, a patent application in the family of I-SceI Patents (*see* Ex. G) with the same named inventors as the '605 Patent, the examiner asserted a reference by Plessis *et al.* against claims directed to a "method of inducing at least one site-directed double-strand break ***in DNA of a cell***, said method comprising[:] providing cells containing double-stranded DNA, wherein said DNA comprises at least one I-SceI restriction site." (US Application 08/336,241 at 94, Ex. H; '241 Application File History, Office Action, dated April 30, 1996, Ex. I, at 3-4 (emphasis added).) In response, the inventors of the '605 Patent amended the claim to recite that "the DNA is chromosomal DNA" and stated that because "Plessis et al. does not teach the I-SceI recognition site on a chromosome ... Applicants have obviated the rejection." ('241 Application File History, Amendment and Response dated August 26, 1996, Ex. J, at 4.) Similarly, during the prosecution of USSN 08/643,732, another patent application in the family of I-SceI Patents (*see* Ex. G) with the same named inventors as the '605 Patent, the examiner asserted the Plessis *et al.* reference against claims directed to a "method of inducing at least one site-directed double-strand break ***in DNA of a cell***, said method comprising[:] providing cells containing double-stranded DNA, wherein said DNA comprises at least one I-SceI restriction site" ('732 Application File History, Office Action, dated March 24, 1997, Ex. K, at. 7-8 (emphasis added).) In response, the inventors of the '605 Patent again amended the claim to recite "in chromosomal DNA" and stated that the "Plessis et al. reference only teaches a yeast ***plasmid*** carrying an I-SceI site . . . The claims in this

application recite '***chromosomal***' DNA." ('732 Application File History, Amendment and Response, dated September 24, 1997, Ex. L. at 2, 23 (emphasis added).) In neither instance did the inventors assert that the "DNA of a cell" is limited to chromosomal DNA. Instead, the inventors amended the claim to specify expressly that chromosomal DNA was intended. Therefore, when the inventors wanted to limit the scope of their claims to "chromosomal DNA" they did so expressly. Cellectis should now be precluded from arguing that almost identical language in Claim 1 of the '605 Patent ("DNA of an organism" rather than "DNA of a cell") is limited to "chromosomal DNA" in spite of the absence of any evidence in either the claim language, the specification, or the prosecution history to support such a limitation. *Ormco Corp. v. Align Tech., Inc.*, 498 F.3d 1307, 1314 (Fed. Cir. 2007) (considering statements made in prosecution of familial patents in construing claims); *Wang Labs., Inc. v. Am. Online, Inc.*, 197 F.3d 1377, 1384 (Fed. Cir. 1999).

**d) Extrinsic Evidence**

As explained by Dr. Derbyshire, the term "DNA of an organism" would have been understood by a person of ordinary skill in the art in 1992 or 1994 as meaning the "heritable genetic material of an organism." In particular, it was known in the art in 1992 that DNA may be found in lower organisms in both plasmids and chromosomes, and in higher organisms in the chromosomes of the nucleus, or outside the chromosomes in mitochondria or (in plants and algae) in chloroplasts. (Derbyshire Decl., ¶ 111, 114.)

In addition, as set forth above, those of skill in the art in 1992 and 1994 understood the term "site-directed" to distinguish a double-stranded break which is created at a pre-determined location in a DNA molecule from a double-stranded break which occurs at a random location in a DNA molecule. (*See* Section IV.A.5 *supra*.)

**e) Cellectis's Flawed Construction**

Cellectis's proposed construction should be rejected because it unjustifiably seeks to re-write the claims to add the limitation "chromosomal" in an effort to avoid Precision's invalidity arguments,[10] and

[10] Precision contends that every element of Claim 1 of the '605 Patent is shown in each of four references: Quirk *et al.* (1989), Bell-Pedersen *et al.* (1990), Delahodde *et al.* (1989), and Durrenberger and Rochaix (1991). Cellectis

seeks to effectively eliminate the term "site-directed" from the claim as there is nothing in Cellectis' proposed construction which could possibly have the meaning of "site directed."

**2. "Containing at least one Group I intron encoded endonuclease recognition site" [All Claims]**

There are three main differences between the parties' alternative claim constructions: (1) Precision and Cellectis each construe the term "Group I intron encoded endonuclease recognition site" differently, as discussed above (*see* Section IV.A.2 *supra*); (2) Cellectis again seeks improperly to include a limitation to a "chromosome"; and (3) Precision construes the term "containing" as meaning "having inserted," whereas Cellectis construes the term "containing" as meaning "having."

First, for the reasons set forth above, Precision's construction of "Group I intron encoded endonuclease site" is the correct one. (*See* Section IV.A.2 *supra*.)

Second, Cellectis's inclusion of the limitation "chromosomal," is improper for the same reasons set forth above with respect to the term "DNA of an organism." (*See* Section IV.B.4 *supra*.)

Third, with respect to the term "containing," the specification of the '605 Patent, the prosecution history of a related application, and the understanding of those of skill in the art in 1992 or 1994 as evidenced by the published statements by the inventors and employees of Cellectis make clear that a Group I intron encoded endonuclease recognition site would ***not*** be naturally-occurring in the DNA of an arbitrary organism and, therefore, must be inserted.[11]

**a) Claim Language and Specification**

For the DNA of an organism to "contain" a Group I intron encoded endonuclease site, there are only two possibilities: (1) the site must occur naturally in the organism's DNA; or (2) the site must have been

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has argued in related U.S. Patent Office Reexamination Nos. 95/000,427 and 95/000,443 that these references do not show cleavage of chromosomal DNA.

[11] Cellectis's attempt to construe the claims as not requiring insertion of a recognition site is critical to Cellectis's attempt to expand the scope of the '605 Patent to cover Precision's technology because Precision's technology allows an endonuclease to be rationally-designed such that it can cleave a desired sequence in the DNA of an organism, obviating the need to insert a recognition site. Indeed, Cellectis admits as much in a patent application filed in 2004 – at least 10 years after the Patents-in-Suit – and published as WO 2004/067736, in which it stated: "The custom-made meganucleases with new specificity according to the present [invention] abolish the limiting step of introducing the recognition and cleavage site for a natural meganuclease in the method of genetic engineering involving meganucleases." (WO 2004/067736, Ex. M, at 34:15-18.)

artificially inserted. (Derbyshire Decl., ¶ 117.) As the specification teaches, and as Cellectis's technical expert, Dr. Stoddard, readily admits, naturally-occurring Group I intron encoded endonuclease recognition sites are very unlikely to be found even in organisms with genomes as large as the human genome. (Stoddard Decl., ¶52; Stoddard Dep. Tr., Ex. F, at 236:8 – 237:4.) According to the inventors, the expected frequency of an 18 bp recognition site in a random DNA sequence is $(0.25)^{18} = 1.5x10^{-11}$ ('605 Patent, col. 10, lines 17-21), or approximately once in every 69 billion bases. Thus, one would expect a naturally-occurring recognition site to appear once in the equivalent of about 20 complete human genomes. ('605 Patent, col. 10, lines 19-20.) Given the rarity of naturally-occurring recognition sites, therefore, for the method of Claim 1 to have broad utility "in an organism," one of ordinary skill in the art would readily appreciate that the recognition site would have to be inserted. (Derbyshire Decl., ¶ 119.)

In addition, the specification of the '605 Patent repeatedly confirms the need for artificially inserted recognition sites and describes several alternative means for inserting them. For example, it states, "[T]his invention relates to a transgenic organism in which at least one restriction site for the enzyme I-SceI has been inserted in a chromosome of the organism." ('605 Patent, col. 3, lines 60-63.) In addition:

'605 Patent, col. 17, lines 24-32:

> 2. Insertion of Artificial Sites
>
> Given the absence of natural I-SceI sites, artificial sites can be introduced by transformation or transfection. Two cases need to be distinguished: site-directed integration by homologous recombination and random integration by non-homologous recombination, transposon movement or retro-viral infection. The first is easy in the case of yeast and a few bacterial species, more difficult for higher eucaryotes. The second is possible in all systems.

'605 Patent, col. 22, lines 33-54:

> Several strategies can be attempted for the site specific insertion of a DNA fragment from a plasmid into a chromosome. This will make it possible to insert transgenes at predetermined sites without laborious screening steps. Strategies are:
>
> 1—Construction of a transgenic cell in which the I-SceI recognition site is inserted at a unique location in a chromosome. Cotransformation of the transgenic cell with the expression vector and a plasmid containing the gene of interest and a segment homologous to the sequence in which the I-SceI site is inserted.
>
> 2—Insertion of the I-SceI recognition site next to or within the gene of interest carried on a plasmid. Cotransformation of a normal cell with the expression vector carrying the synthetic I-SceI gene and the plasmid containing the I-SceI recognition site.
>
> 3—Construction of a stable transgenic cell line in which the I-SceI gene has been integrated in the genome under the control of an inducible or constitutive cellular promoter. Transformation of the cell line by a plasmid containing the I-SceI site next to or within the gene of interest.

(*See also* '605 Patent, col. 18, lines 11-20, col. 21, lines 53-67.)

In fact, ***nowhere*** in the '605 Patent is there an example or a suggestion of using a naturally-occurring Group I intron encoded endonuclease site. To the contrary, as Cellectis's expert, Dr. Stoddard, acknowledged, every example provided in the '605 Patent involves the use of an artificially-inserted recognition site. (Ex. F, at 259:3 – 262:9.) The claim must be limited in accordance with the scope of this disclosure. 35 U.S.C. § 112; *Verizon Servs. Corp. v. Vonage Holdings Corp.*, 503 F.3d 1295, 1308 (Fed. Cir. 2007) (holding that where a patent describes the features of an invention as a whole, this description limits the scope of the invention).

**b) Prosecution History**

In addition, the inventors' statements during prosecution of a related patent application demonstrate that they intended the word "containing" to mean that a recognition site would be inserted. As described above (*see* Section IV.B.1.c *supra*), during prosecution of the related '732 Application, the examiner asserted a reference by Plessis *et al.* against claims directed to a "method of inducing at least one site-directed double-strand break in DNA of a cell, said method comprising[:] providing cells ***containing*** double-stranded DNA, wherein said DNA comprises ***at least one I-SceI restriction site***" (Ex. K at 7-8 (emphasis added).) In response, the inventors stated that because "[n]o natural I-SceI site is known to exist in mammals[,] DNA comprising the I-SceI site ***must be inserted*** in these cells." (Ex. L. at 23 (emphasis added).) Thus, the inventors argued that the claim language "containing . . . at least one I-SceI restriction site" means that a site ***must be inserted*** because such sites do not exist naturally. Therefore, Cellectis should now be precluded from arguing that almost identical language in Claim 1 of the related '605 Patent – "containing at least one Group I intron encoded endonuclease recognition site" – does not require insertion of a recognition site when no recognition site will exist in the vast majority of species. *Ormco Corp. v. Align Tech., Inc.*, 498 F.3d 1307, 1314 (Fed. Cir. 2007) ("When the application of prosecution disclaimer involves statements from prosecution of a familial patent relating to the same subject matter as the claim language at issue in the patent being construed, those statements in the familial application are relevant in construing the claims at issue.").

**c) Extrinsic Evidence**

Finally, numerous statements by both the inventors of the Patents-in-Suit as well as Cellectis's own scientists make clear that the technology described in the I-SceI Patents, including the '605 Patent, requires the insertion of a recognition site into the DNA of an organism:[12]

1. Choulika*†, Perrin*, Dujon* and Nicolas* (1995), Ex. N, at 1973:

> The limitation of the I-SceI system is that the I-SceI site must first be targeted to the chromosome.

2. Epinat†, Arnould†, Chames†, Rochaix†, Desfontaines†, Puzin†, Patin†, Zanghellini†, Paques† and Lacroix† (2003), Ex. O, at 2952 (emphasis added):

> Meganuclease-induced gene targeting has, however, one major limitation: the target locus must contain a meganuclease cleavage site. Therefore, ***as a first step in all current applications, it is required to introduce that cut site***.

3. Arnould†, Bruneau†, Cabaniols†, Chames†, Choulika*†, Duchateau†, Epinat†, Gouble†, Lacroix†, Paques†, Perez-Michaut†, Smith†, and Sourdive† (2004), Ex. M, at 3, lines 5-12, 24-27:

> It has been shown that induction of double stranded DNA cleavage at a specific site in chromosomal DMA [sic] induces a cellular repair mechanism which leads to highly efficient recombinational events at that locus. . . .
>
> Unfortunately, this method of genome engineering by induction of homologous recombination by a double stranded break is limited by ***the introduction of a recognition and cleavage site of a natural meganuclease at the position where the recombinational event is desired***.

*Id.* at 34, lines 8-18 (emphasis added):

> - ***Use of the meganuclease according to the invention***
>
> * * *
>
> The ***custom-made meganucleases*** with new specificity according to the present [invention] ***abolish the limiting step of introducing the recognition and cleavage site for a natural meganuclease*** in the method of genetic engineering involving meganucleases.

4. Arnould†, Chames†, Perez†, Lacroix†, Duclert†, Epinat†, Stricher, Petit†, Patin†, Guillier†, Rolland†, Prieto, Blanco, Bravo, Montoya, Serrano, Duchateau† and Paques† (2006), Ex. P, at 443 (emphasis added):

> Meganucleases are by definition sequence-specific endonucleases with large (>12bp) cleavage sites and they can be used to achieve very high levels of gene targeting efficiencies in mammalian cells and plants, making meganuclease-induced recombination an efficient and robust method for genome engineering. ***The major limitation of the current technology is the requirement for the prior introduction of a meganuclease cleavage site in the locus of interest.***

[12] Authors with asterisks (*) are inventors of at least one of the Patents-in-Suit. Authors with obelisks (†) are current or former employees of Cellectis.

5. Paques† and Duchateau† (2007), Ex. Q, at 54 (emphasis added):

> **Further Developments with I-SceI in Cells**
>
> ***In the nineties***, the growing body of data resulting from the use of I-SceI in a variety of cell types and organisms had clearly demonstrated the robustness of the technology. However, ***the use of I-SceI was dependent on the prior introduction of an 18 bp target sequence*** in the gene of interest, which limited the applications in many fields, and closed the door for any therapeutic applications.

It is plain, therefore, that one of ordinary skill in the art at the time the applications for the Patents-in-Suit were filed would have interpreted Claim 1 of the '605 Patent to require that a recognition site has been inserted and the claim language of the '605 Patent should be construed in accordance with that understanding. (*See also* Derbyshire Decl., ¶ 119.)

**3. "At a/the location in the DNA of the cell" [All Claims]**

Precision's proposed definition that "at a/the location in the DNA of the cell" means "a/the position at which the recognition site is inserted in the DNA of the cell" is appropriate for the reasons set forth in the preceding section. Cellectis's proposed definition "at a/the location in the chromosomal DNA of the organism's cell" is improper for the reasons set forth above. (*See* Section IV.B.1 *supra*.)

**4. "In the DNA of an organism" / "in the DNA of the cell" / "into said DNA of said cell" [All Claims]**

For the reasons set forth above, Precision's construction of the terms "in the DNA of an organism" / "in the DNA of the cell" / "into said DNA of said cell" is the correct one. (*See* Section IV.B.1 *supra*.)

**5. "At a unique location in the genome"**

For the reasons set forth above in connection with the term "inserted at a unique location in the chromosome," Precision's construction of the term "at a unique location in the genome" is the correct construction. (*See* Section IV.A.6 *supra*.)

## V. CONCLUSION

For the foregoing reasons, Precision respectfully requests that the Court construe the disputed limitations of the Patents-in-Suit as proposed herein.

This the 2nd day of November, 2009.

/s/ Robert J. Morris
Robert J. Morris
N.C. State Bar No. 15981
jmorris@smithlaw.com
SMITH, ANDERSON, BLOUNT,
DORSETT, MITCHELL & JERNIGAN, LLP
2500 Wachovia Capitol Center
Post Office Box 2611
Raleigh, North Carolina 27602-2611
Telephone: (919) 821-1220
Facsimile: (919) 821-6800

David B. Bassett
david.bassett@wilmerhale.com
WILMERHALE LLP
399 Park Avenue
New York, New York 10022
Telephone: (212) 230-8800
Facsimile: (212) 230-8888

Vinita Ferrera
vinita.ferrera@wilmerhale.com
Allen C. Nunnally
allen.nunnally@wilmerhale.com
WILMERHALE LLP
60 State Street
Boston, Massachusetts 02109
Telephone: (617) 526-6000
Facsimile: (617) 526-5000

Attorneys for Defendant
Precision BioSciences, Inc.

**CERTIFICATE OF SERVICE**

I hereby certify that, on the 2nd day of November, 2009, I electronically filed the foregoing Defendant Precision BioSciences, Inc.'s Opening Memorandum in Support of Its Proposed Claim Construction with the Clerk of Court using the CM/ECF system, which will send notification to the attorneys of record for Cellectis SA as follows:

| | |
|---|---|
| James L. Gale | jim.gale@smithmoorelaw.com<br>nancy.tackett@smithmoorelaw.com<br>prichter@kenyon.com<br>pharkins@kenyon.com |
| Kelly Tillotson Ensslin | kelly.ensslin@smithmoorelaw.com<br>jeanne.foley@smithmoorelaw.com |

/s/ Robert J. Morris
Robert J. Morris
N.C. State Bar No. 15981
jmorris@smithlaw.com
SMITH, ANDERSON, BLOUNT, DORSETT, MITCHELL & JERNIGAN, LLP
2500 Wachovia Capitol Center
Post Office Box 2611
Raleigh, North Carolina 27602-2611
Telephone: (919) 821-1220
Facsimile: (919) 821-6800